SCIENTIFIC REPORT

Multifocal ERG in ethambutol associated visual loss

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Aim: To determine the anatomical site and extent of electrophysiological dysfunction in patients with ethambutol associated visual loss.

Methods: A comparative case series. Four patients with ethambutol associated visual loss underwent multifocal electroretinography (mERG). Two patients had advanced visual loss while two had early signs of toxicity. The N1-P1, N1, P1 amplitudes, N1, and P1 latencies were compared to 10 age and sex matched controls.

Results: mERG abnormalities were detected in the ethambutol treated patients. The N1 amplitude was significantly lower in the ethambutol treated patients than in the control group.

Conclusion: Ethambutol is possibly toxic to the retina, and not only the optic nerve. The multifocal ERG may be of value to diagnose and monitor patients taking ethambutol.

Ethambutol is commonly used for the treatment of tuberculosis and Mycobacterium avium complex (MAC) infections. It has been associated with optic neuropathy,[1][2] colour vision abnormalities, and visual field defects.[3–5] Ocular toxicity is dose and duration dependent with the incidence as high as 6% in patients receiving more than 15–25 mg/kg/day.[6][7]

We used multifocal electroretinography (mERG) to test four patients diagnosed with ethambutol ocular toxicity and compared them to normal age and sex matched control subjects. Our aim was to is investigate whether there is electrophysiological dysfunction at the level of photoreceptors and outer plexiform layer (outer retina). Ethambutol toxicity has so far been associated mainly with optic nerve damage (inner retina).[1][2][8]

PATIENTS AND METHODS

Multiple retinal areas were stimulated to record local retinal responses with the mERG technique using the Veris 4.8 software (Veris; Electro-Diagnostic Imaging, San Mateo, CA, USA). Fixation was carefully monitored throughout the test procedure. The fixation target was enlarged for subjects who had poor vision. Segments with large eye movements, losses of fixation, or blinks were discarded and re-recorded.

Patient 1

A 60 year old woman presented with complaints of "visual blurring" and "intolerance to bright lights" in both eyes a month after beginning ethambutol (13.65 mg/kg per day) for a recurrent pulmonary MAC infection.

Visual acuity was 20/25 in each eye. She had normal colour vision, and her anterior segment examination was unremarkable. Both pupils were sluggish to direct light stimulation with no relative afferent pupillary defect (RAPD). Fundus examination showed normal discs and maculae. Using the Humphrey10-2 program, an early central defect was found in the right eye and a centrocaecal defect in the left eye. The

mERG waveforms were decreased in amplitude in both eyes to pattern stimuli (fig 1)

Ethambutol was discontinued and 6 months later the visual acuity was 20/20 in each eye, her colour vision was full and her visual fields were normal. Repeated mERG showed a persistent decrease in amplitudes in both eyes with delayed latencies to pattern stimuli (fig 2).

Patient 2

An 80 year old woman presented with decreased vision in both eyes for 3 weeks. She was being treated with ethambutol (15 mg/kg per day) for 7 months for a pulmonary MAC infection. Visual acuity was counting fingers in each eye. Examination of the anterior segment was normal. The pupillary light reactions were sluggish bilaterally with a left RAPD. Visual field testing by confrontation showed dense central scotomas bilaterally; visual acuity was too poor for formal visual field testing. She had pale optic nerve heads bilaterally. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and orbits were normal.

Multifocal ERG results showed diffuse reduction in the amplitudes, especially in the central area (fig 3) She was seen 4 months after discontinuation of ethambutol and her vision had improved to 20/100 right eye and 20/40 left eye. Repeat mERG still showed decreased amplitudes, and diminished foveal peaks. There was no appreciable change compared to the first mERG (fig 4).

Patient 3

A 66 year old man who was diagnosed 5 months earlier with MAC pulmonary infection and was started on ethambutol (15 mg/kg per day) presented with a complaint of "objects looking too bright" and "difficulty of adjusting from bright to dim light conditions." Visual acuity was 20/30 in the right and 20/20 in the left eye. Colour vision was normal in both eyes. Slit lamp examination was unremarkable. The pupils were normal with no RAPD. Fundus examination showed normal discs and maculae. Automated static perimetry (Humphrey 24-2) was normal, but a using a Humphrey 10-2 program, there was one area of depression in the right eye. Full field ERG was normal in both eyes. mERG demonstrated decreased amplitudes and reduced foveal peaks in both eyes to pattern stimuli (fig 5).

Patient 4

A 75 year old woman noticed worsening of vision after undergoing cataract surgery in the left eye. She had been on ethambutol, isoniazid and rifampin for a pulmonary MAC infection. Visual acuity was counting fingers at 2 feet in the right and at 6 feet in the left eye. She identified only the test plates of the Ishihara pseudoisochromatic plates in each eye. Slit lamp examination was unremarkable. The pupils were

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Abbreviations: CT, computed tomography; ERG, electroretinography; MAC, Mycobacterium avium complex; mERG, multifocal electroretinography; MRI, magnetic resonance imaging; RAPD, relative afferent pupillary defect
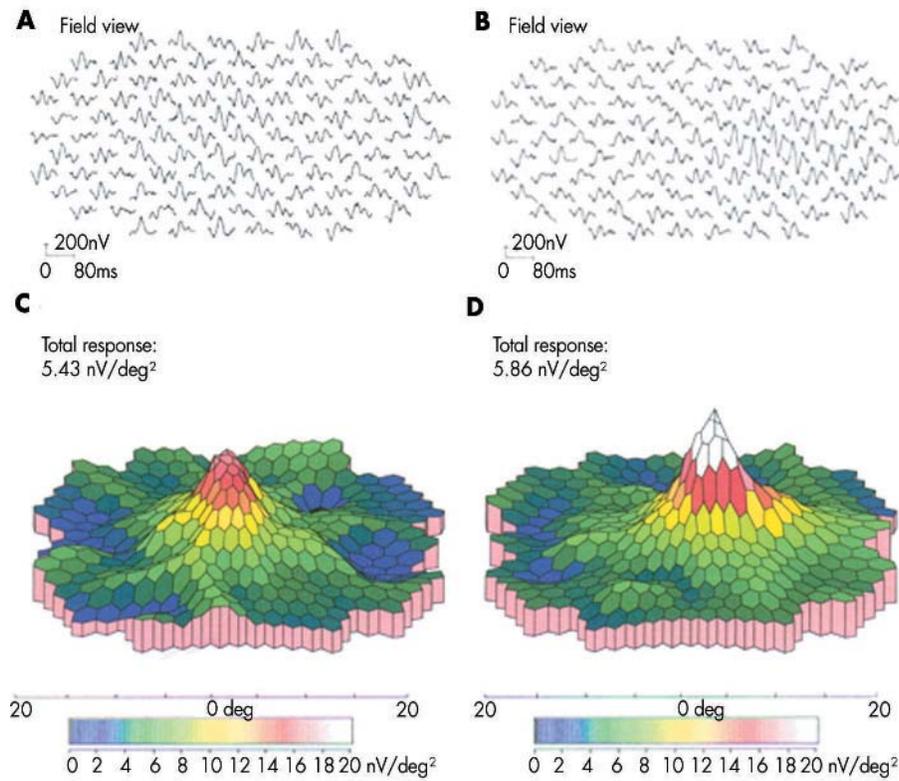
A Field view

B Field view

200nV

0   80ms

200nV

0   80ms

C

Total response:
5.43 nV/deg²

D

Total response:
5.86 nV/deg²

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

Figure 1 Trace arrays showing subnormal mERG with decreased amplitudes in the both eyes. In (A) the right eye, and (B) the left eye, there are decreased amplitudes in the central area. The three dimensional topography map shows blunted foveal peaks more in the right (C) than the left eye (D).
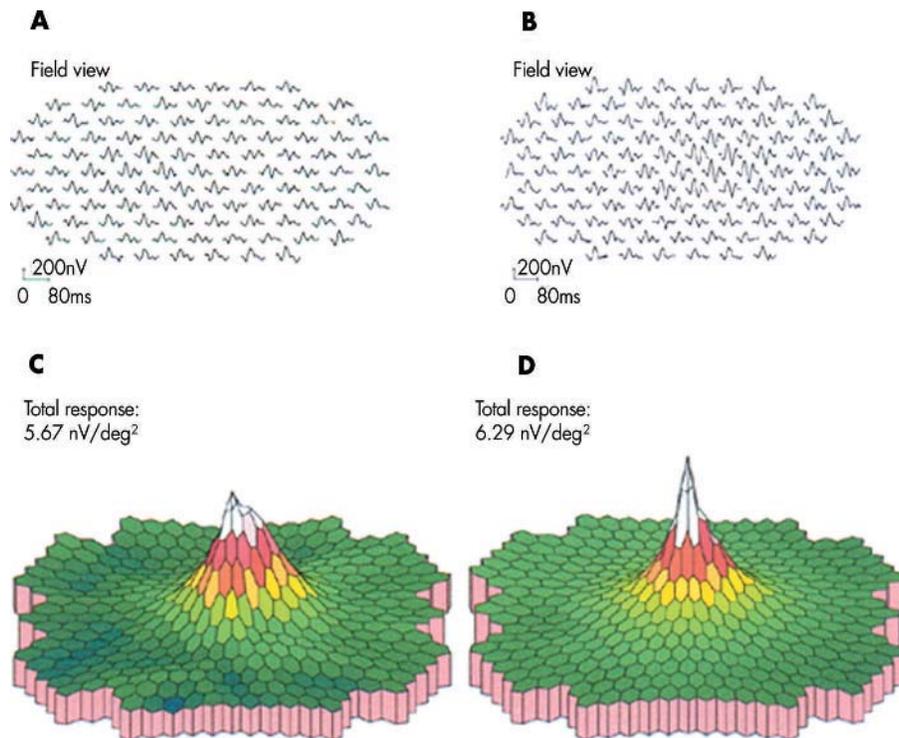
A

Field view

B

Field view

200nV

0   80ms

200nV

0   80ms

C

Total response:
5.67 nV/deg²

D

Total response:
6.29 nV/deg²

Figure 2 Trace arrays of multifocal ERG in (A) right and (B) left eyes. Amplitudes are diminished centrally more in the right eye than the left eye. The three dimensional topography map shows blunted foveal peaks more in the right (C) than the left eye (D).
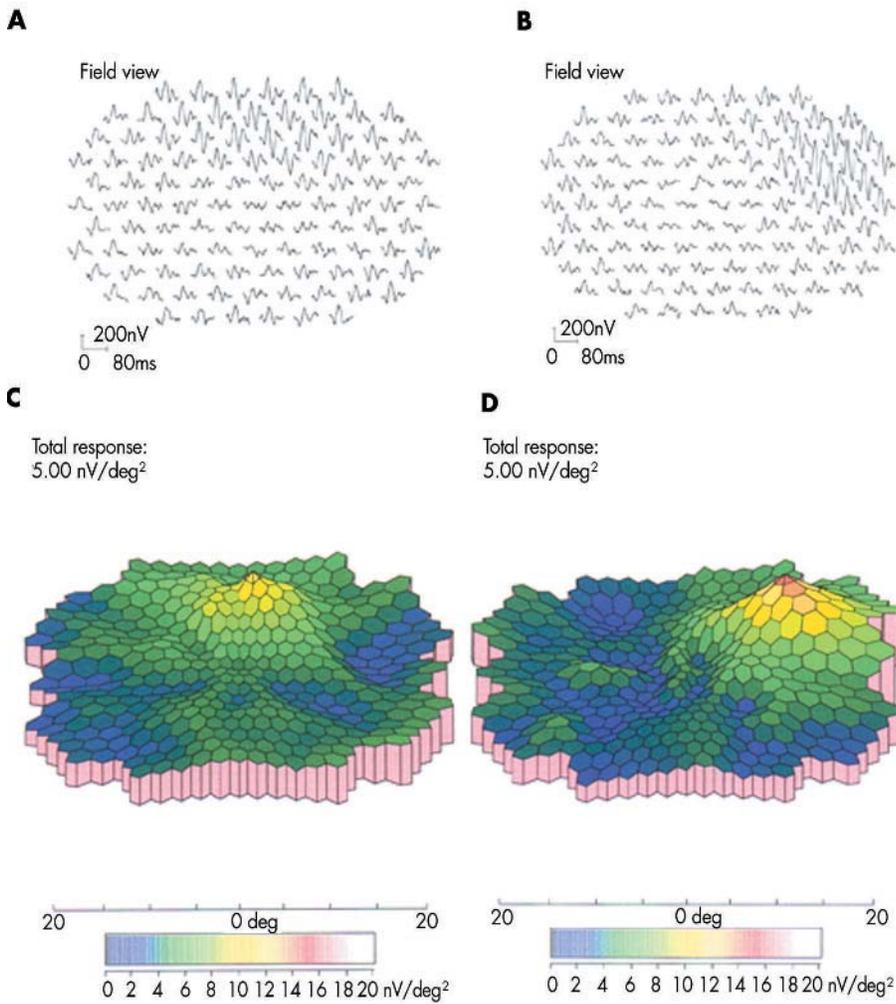
Figure 3 Trace arrays of (A) the right eye and (B) left eye show diminished amplitudes especially in the central areas. The topographic (three dimensional) density plots show blunted foveal peaks in the right (C) and the left (D) eye.

sluggish to light stimulation without an RAPD. Fundus examination showed mild disc pallor with normal maculae.

Automated static perimetry (Humphrey 10-2 program) showed bilateral central scotomas. mERG showed decreased amplitudes to pattern stimuli (fig 6).

Three months after discontinuation of ethambutol, her vision had improved to 20/60 in the right and 20/50 in the left eye. Colour vision improved to five of 11 colour plates in each eye. The mERG was still abnormal (fig 7).

Data analysis
Multifocal ERG
Using Veris 4.8 , first order kernel responses were evaluated for latencies (implicit time) for N1 (first negative trough), P1

Table 1 Responses elicited from ring 1

Category	N1-P1 amplitude (nV/deg^2)	N1 amplitude (nV/deg^2)	P1 amplitude (nV/deg^2)	N1 latency (ms)	P1 latency (ms)
Control	73.04	16.97	31.31	16.04	29.83
Patient	53.91	10.81	25.06	15.62	28.85
p Value	0.223	0.019*	0.43	0.47	0.055

*Wilcoxon rank sum test.

Table 2 Responses elicited from ring 2

Category	N1-P1 amplitude (nv/deg^2)	N1 amplitude (nv/deg^2)	P1 amplitude (nv/deg^2)	N1 latency (ms)	P1 latency (ms)
Control	24.445	8.6	15.78	9.06	15.78
Patient	23.1625	8.28	14.87	8	14.87

A Field view

200nV
0   80ms

Total response:
4.69 nV/deg²

B Field view

200nV
0   80ms

Total response:
4.57 nV/deg²

C

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

D

20   0 deg   20
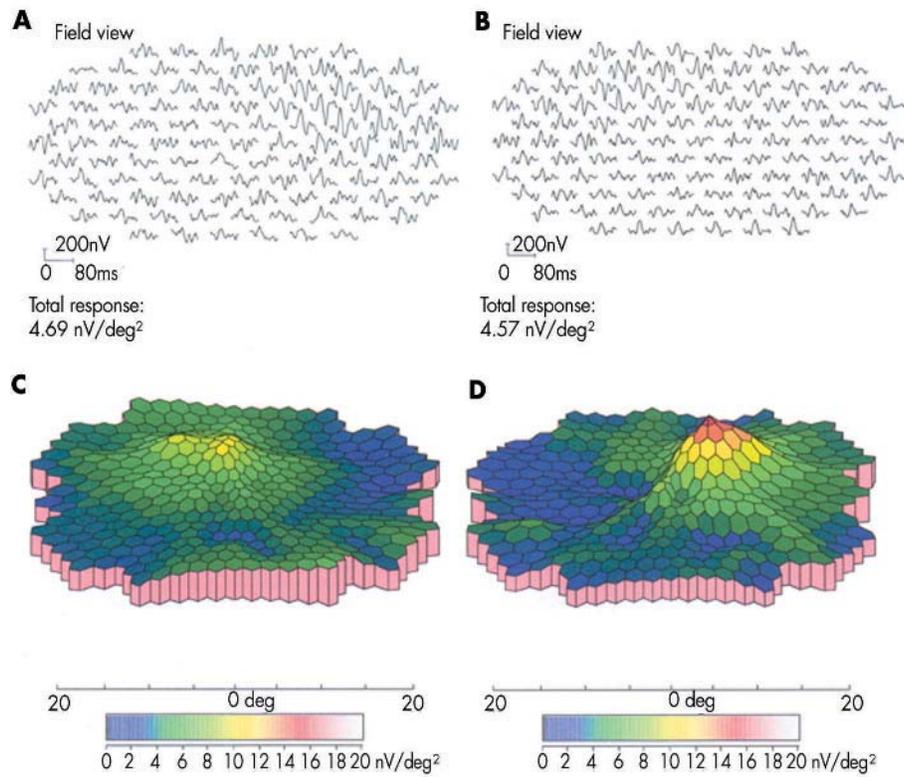
0 2 4 6 8 10 12 14 16 18 20 nV/deg²

Figure 4 Trace arrays of (A) the right eye and (B) the left eye decreased amplitudes centrally. The topographic (three dimensional) density plots show flattened foveal peaks in the right eye (C) and reduced peak in the left eye (D).
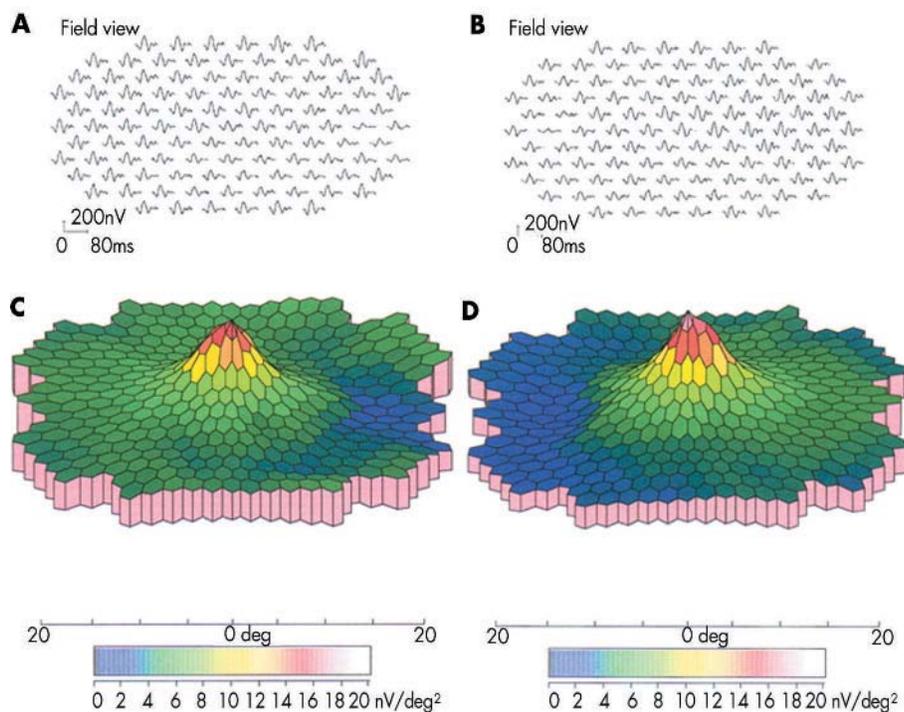
A Field view

200nV
0   80ms

B Field view

200nV
0   80ms

C

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

D

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

Figure 5 Trace arrays of the right eye (A) and left eye (B) showing decreased amplitudes more in the central region of both eyes. The three dimensional topography map shows blunted foveal peaks in the right eye (C) and left eye (D).
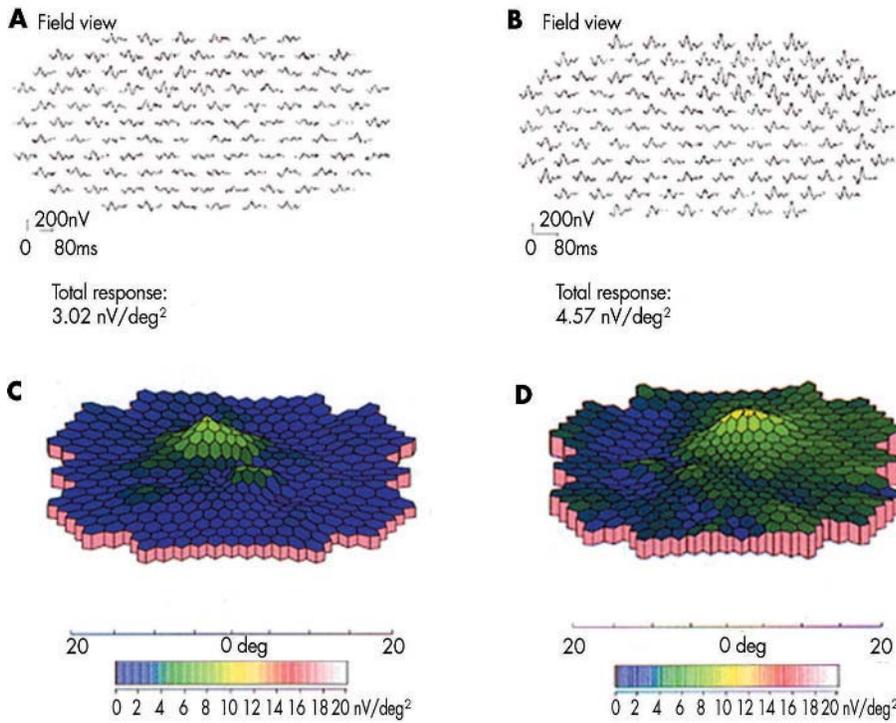
A Field view

200nV

0   80ms

Total response:
3.02 nV/deg²

B Field view

200nV

0   80ms

Total response:
4.57 nV/deg²

C

D

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

Figure 6 Decreased amplitudes in the central region of the right eye (A) and left eye (B). The three dimensional topography map shows blunting of the foveal peaks in both eyes. (C) Right eye, (D) left eye.

(first positive peak); amplitudes N1 (from baseline to the trough of the first negative wave), P1 (from baseline to the peak of the first positive way), and N1-P1 (from the first negative trough to the first positive peak). The responses elicited by the central six hexagons were summated and designated as ring 1 (central 7 degrees, foveal and parafoveal); and the responses from another concentric ring of 16

hexagons were also summated and designated ring 2 (central 10–12 degrees, parafoveal). Because we were looking for a retinal dysfunction in the macular region, we limited the analysis to the responses elicited in those two rings (fig 8). The N1, P1 latencies and the N1-P1, N1, and P1 amplitudes of both eyes were averaged. These were then compared in the ethambutol treated patients to 10 control subjects (six
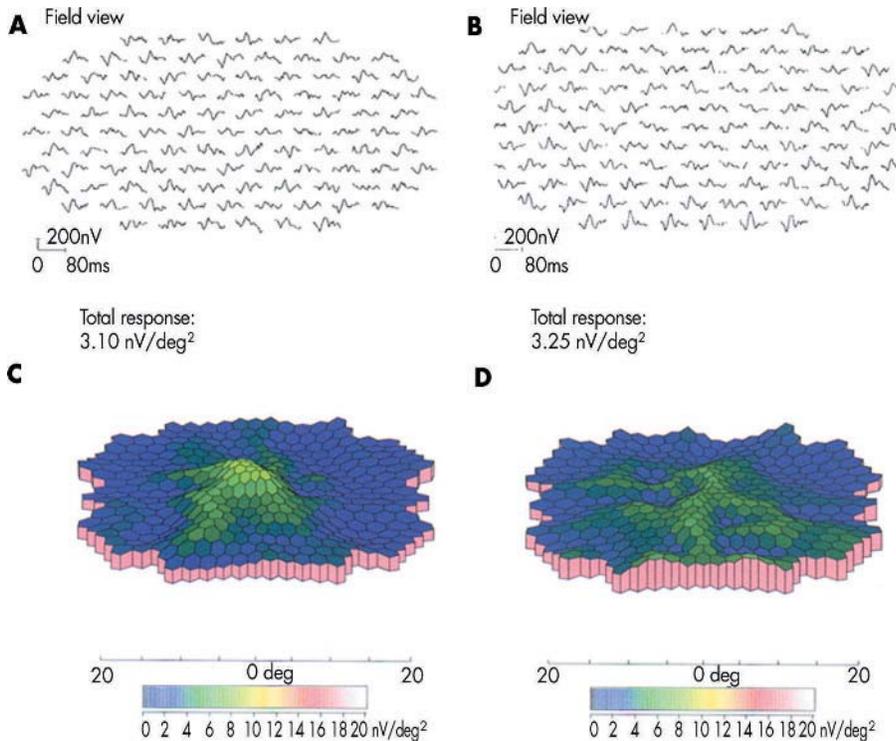
A Field view

200nV

0   80ms

Total response:
3.10 nV/deg²

B Field view

200nV

0   80ms

Total response:
3.25 nV/deg²

C

D

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

20   0 deg   20

0 2 4 6 8 10 12 14 16 18 20 nV/deg²

Figure 7 Four months after the first mERG. The amplitudes are still diminished centrally in both (A) right eye and (B) left eye. The three dimensional map still shows blunting of the foveal peaks. (C) Right eye, (D) left eye.
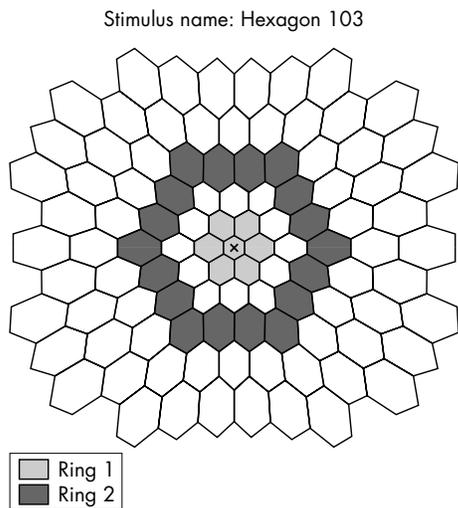
Stimulus name: Hexagon 103

Figure 8 Diagram showing the two rings we tested with Veris 4.8. Ring 1 comprises the six central hexagons in the central 7 degrees, while ring 2 comprises 16 hexagons located 10–12 degrees from the centre.

women and four men) with a mean age of 61.5 (SD 5.75) years using the non-parametric Wilcoxon rank sum test. There was no statistically significant difference between the mean age of the control group and the ethambutol treated patients (p = 0.14). Each one of the control group subjects had a visual acuity of 20/30 or better in one or both eye, and a normal neuro-ophthalmic assessment. In addition, none of the control group subjects was taking any medications that could adversely affect retinal function

RESULTS

The mean N1 amplitude in ring 1 was significantly lower in the ethambutol treated patients than the control group (3.20 versus 9.25 nV/degree ^{2}) (p<0.05) (fig 9). The mean N1-P1 amplitudes, P1 amplitudes, and the mean N1 and P1 latencies in ring 1 were not significantly lower in the ethambutol treated patients compared to the control groups (table 1). There was no significant difference in any of the latencies and the amplitudes in ring 2 between the ethambutol treated patients and the control group (table 2).

DISCUSSION

We have demonstrated mERG abnormalities in patients with presumed ethambutol optic neuropathy. These changes are characterised by a decrease in amplitude with predilection for
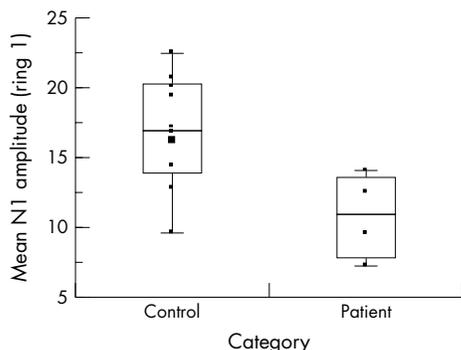

Figure 9 A box plot diagram showing the difference in the mean N1 amplitude in the ethambutol treated patients and the control group. Mean amplitude in nV/deg^2

the central areas (macula). Previous studies have found abnormalities in the visual evoked potentials,[9] full field ERG and EOG in patients with presumed ethambutol optic neuropathy.[10–12] In experiments on fish, ethambutol altered synaptic connections between horizontal cells and cones in a dose related fashion, resulting in degeneration of the cone pedicles.[13]

In our study, the N1 amplitude was found to be significantly lower in the ethambutol treated patients compared to age matched controls. The source of the multifocal ERG signals, as in full field ERG, is thought to be from the outer retina with very little contribution from the inner retina (ganglion cell layer).[14 15] Therefore, for a disease to decrease the amplitude of the mERG, the cone photoreceptors or cone driven bipolar cells must be abnormal. Although there was a statistically significant difference only between the N1 amplitude of the patients and control subjects, it is possible that our patient group comprised patients in various stages of ethambutol toxicity. In fact, when we compared the N1-P1, and P1 amplitudes of patients 2 and 4 (advanced toxicity) with the control group, they were significantly lower (p = <0.05). These two patients, however, were also older than patients 1 and 3. It still is possible though that given enough time, N1-P1 and P1 amplitudes would eventually be affected in the other patients.

Because of the small sample size of this study, it is difficult to reach a definite conclusion about our observations. Although an abnormal mERG can be caused by eccentric fixation, either voluntary (functional visual loss) or because of a small central visual field loss caused by optic atrophy, fixation was meticulously monitored during testing in all patients.

With the resurgence of tuberculosis, especially in the immunocompromised group, and the increasing reports of MAC pulmonary infections even in immunocompetent[16 17] and elderly women with no predisposing factors,[18] prompt diagnosing of ethambutol toxicity can be important in preventing permanent visual loss. We believe our findings merit re-examining the widely accepted notion that ethambutol causes primarily optic neuropathy. Future studies with a larger sample size are needed to determine the early stages and the natural history of retinal toxicity caused by ethambutol.

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The authors have no proprietary interest in any of the instruments used or any other aspect of this study.

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